PHARMACOKINETIC MODELING
MODEL DEVELOPMENT

This chapter presents the formulation of the models used to establish the concentration pattern within the human body due to the toxic chemicals exposure. Two types of models are developed. The first one is a single compartment model in which the body is considered to be a single compartment as the toxic chemicals is instantaneously dispersed within the body. The other is a two compartment model in which the rate of dispersion of toxic chemicals in the human body is moderate. In developing the models, the fluctuations in the concentrations of toxic chemicals due to variable dosing are also considered.

Concepts of compartments

The concept of compartment is often difficult to grasp. The body, in reality, is composed of a very large number of compartments. Each cell and part is, in a sense, a small compartment. However, in pharmacokinetics, a compartment refers to those organs and tissues for which the rates of uptake and subsequent clearance of a chemical are similar.

Models are used to describe and interpret a set of data obtained by experimentation. A model in pharmacokinetics is a hypothetical structure, which can be used to characterize with reproducibility the behavior and the "fate" of a chemical in biological systems when given by a certain route of administration and in a particular dosage form.

A compartment is an entity, which can be described by a definite volume and a concentration (of the chemical contained in the volume). Usually the behavior of a chemical in biological systems can be described by a one compartment model or a two compartment model. Sometimes it is necessary to employ multi-compartment models.

Actually, the human body is a multi-million compartment model considering chemical concentration in different organelles, cells or tissues. However, in the living body we have access to only two types of body fluid - blood (or plasma or serum) and urine. Compartment models in pharmacokinetics are, therefore, used to fit experimental data from blood level versus time curves or urinary cumulative excretion versus time curves to models.

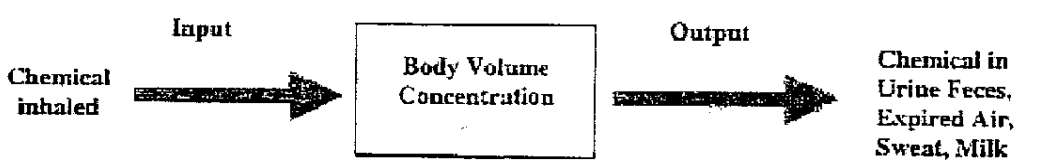
Two or more compartments can be linked together because a chemical may move from one compartment into another and back. The movement occurs at different rates (speeds) and is described by distribution rate constants.

For developing both the models, following assumptions were made:

- The person exposed to toxic chemicals is a normal person of normal body weight of 70 kg.
- There is no concentration build up of toxic chemicals within the body after the inhalation of toxic chemicals.
- The saturation concentration of the toxic chemicals within the body is not considered.

One Compartment Model

If the chemical entering the body (input) distributes (equilibrates) instantly between the blood and other body fluids or tissues, then one compartment model can be used to model the concentration pattern. In the one compartment model, the chemical is not necessarily (and indeed is rarely) confined to the circulatory system. The chemical may occupy the entire extra cellular fluid "soft" tissue or the entire body; however distribution occurs instantly and is not "pooled" in a specific area.



BASIC ONE COMPARTMENT MODEL

The toxic chemical's absorption into the human body is from inspired air. A one compartment model is developed using the rate of change of concentration of a toxic chemical in the body to its rate of absorption from inhaled air minus its rate of elimination.

$$\frac{dC}{dt} = F\frac{Q}{V_b}C_a - k_{el}C$$

where,
dC/dt=change of concentration of toxic chemical inside the human body per unit time.
F=bioavailability (a ratio of the mass of toxic chemical absorbed by the body to the mass of toxic chemical in inhaled air)
Q=volumetric flow rate of inhaled air
V_b=volume of blood in which the toxic chemical is stored
C_a=ambient air concentration
k_{el}=elimination rate
C= concentration of the toxic chemical inside the human body

In order to obtain the variation of C with time, the above equation can be integrated as follows:

$$\int\left[\frac{dC}{dt}+k_{el}C\right]=\int F\frac{Q}{V_b}C_a$$

After integration of the above equation, one obtains

$$C=Ae^{-k_{el}t}+\frac{1}{k_{el}}F\frac{Q}{V_b}C_a$$

where, A is a constant of integration and may be obtained using initial condition at t = 0, C = C_o

$$C=C_oe^{-k_{el}t}+\frac{1}{k_{el}}F\frac{Q}{V_b}C_a(1-e^{-k_{el}t})$$

[Note: at t = 0, C = C_o $\therefore C_o-\frac{1}{k_{el}}F\frac{Q}{V_b}C_a=A$

The half time (half-life) or $T_{1/2}$

The half-time ($T_{1/2}$) is the time taken for the concentration of toxic chemicals in the blood or plasma to decline to half of its original value.
The elimination rate constant (k_{el}) is a constant, which is more useful to the pharmacokineticist, and it can be obtained by simple calculation from $T_{1/2}$. It is a proportionality constant, and may be defined as the fraction of toxic chemicals present at any time which would be eliminated in unit time. For example, if k_{el} is 0.1 min^{-1}, 10 percent of the toxic chemicals present at any instant in time would be eliminated in one minute.

When the concentration of toxic chemicals in plasma (C_p) or blood declines to half of its original value, the relationship is:

$C_p / C_o = 0.5$
or, more generally, in the case of a linear $\log_{10} C_p$ versus t plot:

$$\frac{C_{P_t}}{C_{(t-T_{1/2})}}=0.5$$

where,
C_{Pt} is the concentration at time t
$C_{(t-T1/2)}$ is the concentration at a time $T_{1/2}$ earlier than t.

Since $dC_p/dt = -k_{el}C_p$

Integrating the above equation from t = 0 to t and $C_p = C_o$ to C_p, one obtains

$$\ln C_P = \ln C_0 - k_{el}\, t$$

i.e. $$\ln\left(\frac{C_p}{C_0}\right) = -k_{el}t$$

and $C_P / C_o = 0.5$ when $t = T_{1/2}$
then $\ln 0.5 = -k_{el} T_{1/2}$
since $\ln 0.5 = 0.693$

$$T_{1/2} = 0.693 / k_{el}$$

or

$$k_{el} = 0.693 / T_{1/2}$$

From a linear $\log_{10} C_P$ versus t plot we can obtain $T_{1/2}$ and therefore the elimination rate constant (k_{el}). k_{el} has the dimensions of h^{-1}, min^{-1}, or s^{-1} depending on whether $T_{1/2}$ is in hours, minutes or seconds respectively.
After estimating the value of k_{el} from half-life using above equation, concentrations within the human body can be estimated as:

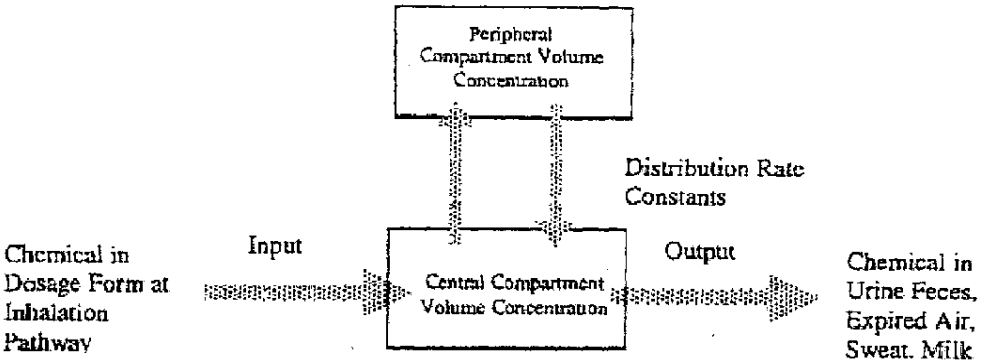
$$C(t) = C_o e^{-k_{el}t} + \frac{1}{k_{el}} F \frac{Q}{V_b} C_a (1 - e^{-k_{el}t})$$

where,
C(t) = concentration at time t
C_o = initial concentration of chemical inside the body
k_{el} = elimination rate constant.

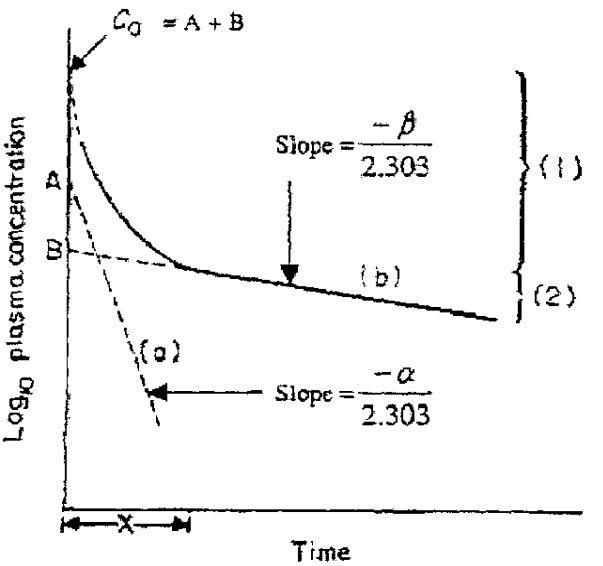
The difficulty in applying the equation for C(t) is the values of F and V_b. Bioavailability of a chemical may be obtained from literature. However, the volume of blood V_b involved in the storage of chemical should be obtained from experiments.

Two Compartment models

If the toxic chemicals entering the body (input) does not instantly distribute evenly (equilibrate) between the blood and those other body fluids or tissues which it eventually reaches, then the two compartment model can be used to predict its behavior within the body. The distribution of the toxic chemicals in blood and other "soft" tissues, on one hand, and into other "deep" tissues, on the other hand occurs at different rates (speeds). Eventually a steady state will be reached which terminates the "distribution" phase. However, from such data it cannot be necessarily said to which specific tissues or organs a toxic chemicals was slowly distributed. It can be postulated from the pKa value and lipid/water partition coefficient. However, a definite answer may be obtained only by biopsy, animal experiments, the use of radioactive materials and whole body scintillation. The body fluids or tissues, which are in equilibrium with the circulatory system, comprise the central compartment which is accessible through blood sampling. Those body fluids or tissues into which the chemical distributes slowly comprise the peripheral compartment, which is not accessible by blood sampling.



According to an experiment conducted by Clark and Smith (1981), the concentration vs. time curve was not exponential for the entire length. The figure shows the plasma concentration measured after an i.v. bolus dose. The plot is semi-logarithmic. The experimental points lie on the solid line in the plot. The plasma level decline can be clearly divided into two phases, (1) and (2) as shown in Figure below,



The first phase (1) represents the distribution of the toxic chemicals from the central compartment, in this case the plasma and rapidly distributed tissues, into a second compartment. Equilibrium will be attained between the two compartments after a certain time period and two compartments behave essentially as one. This can be clearly stated as the graph moves into a log/linear phase (2). This is represented by line (b). This log/linear phase represents the elimination from the central compartment in equilibrium with the second compartment. The slope of line (b) is used for determination of a rate constant (β). This is calculated by a method analogous to the method for calculating k_{el} in the one compartment model.

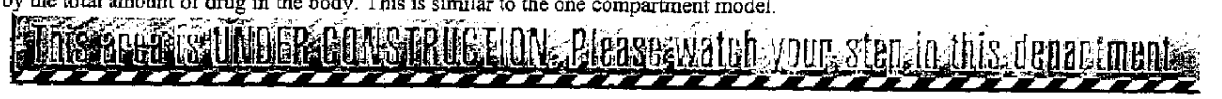
This rate constant is normally referred to as a hybrid rate constant since it is a complex value related to several individual constants. It is the rate constant which governs the overall elimination rate of the toxic chemicals. The half-life, which can be calculated in this case from the rate constant β, is often termed as the biological half-life.

The zero-time intercept B represents the apparent concentration if the toxic chemicals has been distributed instantaneously throughout both the central and second compartments. Thus, intercept B can be used to calculate as apparent volume of distribution (VD). Volume terms with a two compartment model are not as useful as in one compartment model. Line (a) is resulted when CP values which lie on

line (b) are deducted from the real values of C_p. Thus, line (a) represents these differences. The slope of line (a) is used to determine another rate constant (α). The method of calculation is again similar to the method which has been discussed before. This rate constant α is also a hybrid rate constant and it is the constant which governs distribution of the drug into the second compartment.

Another zero-time intercept A can also be determined. If intercept A is added to intercept B, C_0 is obtained which is the theoretical concentration of the toxic chemicals in plasma at time zero. This value can be used to calculate the volume into which the drug is initially introduced (i.e. the volume of the central compartment, V_C).

The hybrid rate constant β, and the elimination rate constant, k_{el}, are closely related. In many cases elimination takes place only from the central compartment. Therefore, the rate of elimination is governed by the amount of drug in the central compartment rather than by the total amount of drug in the body. This is similar to the one compartment model.



Incorporation of Concentration Fluctuations

The above developed models are valid for a uniform C_a over time. However, the ambient concentration vary with time. A simple procedure is suggested below to account for the variation over time.

1. Calculate C(t) using C_o and C_a for the first time step.
2. The calculated value of C(t) in step1 will become C_0 for the second step. The new value of C_a will be used for the calculation of C (t) for this step.

The above procedure can be repeated over the entire time duration to obtain C(t) for different values of time.

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Drop in your comments and suggestions to:

- Ashok Kumar, akumar@uoft02.utoledo.edu
- Kalyanakrishnan Venkataraman, kvenkata@eng.utoledo.edu